Exhibit F

SUPPLEMENTAL REPORT OF PEGGY PENCE, PhD, RAC, FRAPS
RE: TENSION FREE VAGINAL TAPE (TVT) SYSTEM
AND
MODIFIED GYNECARE TVT OBTURATOR SYSTEM
PRODUCT LIABILITY LITIGATIONS
vs. ETHICON, INC.
AND JOHNSON & JOHNSON
(Collectively referred to in this Report as Ethicon)

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TABLE OF CONTENTS

I. REPORT OBJECTIVES

Since the preparation of my October 14, 2013, and June 12, 2014, Tension Free Vaginal Tape System (TVT) Reports and my July 17, 2014, and April 24, 2015 (First Supplemental) Modified Gynecare TVT Obturator System (TVT-O) Reports, I have had an opportunity to review the November 12-13, 2015, deposition of Martin Weisberg, M.D., and associated exhibits. Dr. Weisberg testified as the Ethicon Corporate Designee regarding Revised TVT Instructions for Use (IFUs) and Revised Gynemesh PS IFUs. The purpose of this Supplemental Report is to present information from the stated Ethicon deposition and other pertinent information that provide further support for my previously expressed opinions. I have not changed any of my opinions as a result of my review of these additional materials, nor do I offer any new opinions in this Supplemental Report. Importantly, my prior October 14, 2013, June 12, 2014, July 17, 2014, and April 24, 2015 (First Supplemental) Expert Reports, noted above, are incorporated herein by reference in their entirety, including all opinions expressed therein.

The method and level of scrutiny that I used in preparing this Supplemental Report are the same that I have used in my practice for my entire career as an expert in medical product development, regulatory affairs, and as a scientist, and the same that I used in the preparation of my prior Reports referenced above. To facilitate review and cross-reference to my prior Reports, the supplemental information provided herein is presented in the same order as presented in those Reports.

II. APPLICABLE INDUSTRY STANDARDS (Attached as Exhibit 1 and incorporated as if set forth fully herein)

Globally recognized industry standards for the development of medical devices and, in particular, those relevant to the subject matter of both this Supplemental Report and my prior TVT (October 14, 2013, and June 12, 2014) and TVT-O (July 17, 2014, and April 24, 2015 [First Supplemental]) Expert Reports are described and establish additional foundation for my opinions, notably, other than FDA regulations and guidance.

III. CLINICAL BACKGROUND UNDERLYING OPINIONS: MULTIPLE AUTHORITATIVE BODIES SUPPORT NEED FOR CLINICAL DATA FOR MESH USE IN TRANSVAGINAL STRESS URINARY INCONTINENCE (SUI) REPAIR

The purpose of clinical evaluation of a medical device is to demonstrate that the device complies with the essential principles of safety and performance, including that any adverse events are acceptable when weighed against the benefits of the device's intended performance.[1] This is especially important for a device that is intended to treat quality of life symptoms and for which there are alternative treatments. While clinical evaluation (Reference Exhibit 1, Section II.F.) should be performed premarketing, clinical evaluation also should be conducted periodically throughout the life cycle of the device to (i) analyze the product's risk-benefit ratio in consideration of available clinical safety and performance information and (ii) take actions as

[1] Final Document: Global Harmonization Task Force. Clinical Evaluation, May 2007, Section 1.

appropriate. Among such actions are generation of clinical data to address outstanding issues and the need to include risk information identified in the risk analysis in the Instructions for Use.[2]

Multiple authoritative sources have emphasized the importance of clinical studies to establish the safety and effectiveness of vaginal mesh implants and, accordingly, have expressed concern about the lack of clinical data, in particular, the lack of long-term data to support permanent implantation of vaginal mesh for SUI repair and establish whether the risk-benefit ratio is favorable. Among such authoritative sources are those discussed below.

A. Haute Autorité de Santé (HAS) French National Authority for Health. Evaluation of Mesh Implants Installed Through the Vaginal Approach in the Treatment of Genital Prolapse. Department of the Evaluation of Medical and Surgical Procedures.

At the request of the National College of French Gynecologists and Obstetricians and the French Association of Urology, the French National Authority for Health (HAS) conducted an evaluation of the safety and effectiveness of vaginally implanted mesh for the treatment of genital prolapse.[3] A total of 40 references published in French or English were included in this evaluation (described as: 1 report of a technological evaluation; 1 systemic inspection; 1 descriptive survey of equipment monitoring; 2 open, randomized studies; 1 nonrandom, comparative study; and 34 case studies). The bibliography was not provided in this document. The HAS critical analysis of the publications found that, in general, studies had non- or under-described inclusion criteria, insufficient staff workers, median follow-up that did not exceed two years, outcome criteria that were poorly described or not described at all, and a lack of consistency in the means of evaluation. In most cases, assessments of efficacy and safety were confounded by "associated" procedures (e.g., concomitant surgery for incontinence or second type of prolapse). The types of implants used in these studies (intended use, whether absorbable, method of implant, precut or uncut) were so variable that nearly every study used a unique implant. Anatomical success rates varied from 46%-100%, depending on the type of prolapse, type of implant, definition of "success," and length of follow-up. Functional success based on symptom improvement was not quantifiable due to variability of symptoms measured across studies and use of non-validated questionnaires or scales.

The documentation of complications was very heterogeneous across studies. A 2005 study conducted in France (referred to as a "materiovigilance study") identified erosions, cellulitis, and abscess as the main complications observed following mesh implantation for urinary incontinence and/or vaginal prolapse. The overall estimated frequency for these complications was 8%, with a duration of follow-up of 10 months and rate of re-operation of 92%. The frequency appeared to be higher in cases of prolapse compared with cases of urinary incontinence. Other studies reported erosion rates of 0% to 24.5%, depending on type of implant used and type of prolapse treated. Two studies reported patient deaths, but did not

[2] Final Document: Global Harmonization Task Force. Clinical Evaluation, May 2007, Section 1.
[3] HAS French National Authority for Health —Evaluation of Mesh Implants Installed Through the Vaginal Approach in the Treatment of Genital Prolapse (translated, French to English) November 2006.

evaluate whether the deaths were treatment-related. Other complications reported included pulmonary embolism, hemorrhage, wound dehiscence, rectal or bladder injury, rejection of the implant, hematoma, urinary tract infections, surgical wound infections, pain, dyspareunia, de novo urge or stress urinary incontinence (SUI), and de novo prolapse. Frequencies varied among studies. The report stated that some safety studies did not mention severe infections (presumably whether they occurred or not) and these studies also did not perform frequency analysis of complications. No attempt was made to associate complications with the primary surgical endpoint or concomitant procedures. The report acknowledged that some complications could be attributable to pelvic surgery in general.

These findings generated the following comments by experts retained by HAS:

- Preoperative evaluations and duration of follow-up were insufficient;
- Controlled studies were performed only for absorbable, synthetic meshes, which were associated with high recurrence rates;
- The impact on quality of life of complications such as dyspareunia, pain, retractions, erosions, granulomas and infections was not assessed;
- Given the risks of infection, aseptic surgical conditions are required;
- **Only mesh materials validated by clinical trials should be used**;
- Adverse events should be fully reported.

The **experts concluded that prospective studies should be performed**, including the following elements:

- Pre- and postoperative evaluations using POP-Q classification for anatomical outcome and validated questionnaires for functional outcomes;
- **Medium and long-term follow-up (5 to 10 years)**;
- **Exhaustive documentation of adverse events, including elements that may influence the frequency of erosion**;
- **Evaluation of the management of erosions and retractions**.

(Emphasis added.)

The overall conclusion of this report was that the available data in the literature at the time this report was written did not allow an effective evaluation of the anatomical and functional viability of transvaginally placed implants for the treatment of genital prolapse. Serious complications were identified but their frequency was not able to be determined. **Therefore, the French National Authority for Health concluded that the use of mesh implants for transvaginal correction of genital prolapse remained a matter of clinical research.** It is important to note that the date of this conclusion was November 2006, almost three years after the Modified GYNECARE TVT Obturator System (TVT-O) became available for sale and almost nine years after the Tension Free Vaginal Tape System (TVT) became eligible for sale. (Emphasis added.)

B. United States Food and Drug Administration (FDA) Literature Review and MAUDE Database Review

Similarly to the impetus for the HAS evaluation of the safety and effectiveness of vaginally implanted mesh discussed above, by 2008 FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) concerns raised by the clinical community and citizens, (2) the published literature, and (3) postmarket surveillance of the publicly available MAUDE database for medical device reports (MDRs). In 2008, the MAUDE database showed that more than 1,000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair stress urinary incontinence (SUI) and pelvic organ prolapse (POP). A subsequent review of the MAUDE database covering the 2008-2010 timeframe presented SUI and POP complications separately and identified a total of 2,874 MDRs for urogynecologic surgical mesh, of which 1,371 were associated with SUI repairs; notably, these MDRs were additional to the 1,000 identified previously in the 2008 MAUDE database search for the years 2005-2007, as discussed in my initial Reports. The types of adverse events reported to the MAUDE database during 2008 to 2010 for surgical meshes to treat SUI were death (n=3), injury (n=1131), malfunction (n=236), and "other" (n=1). Of the three deaths reported, two were related to the mesh placement procedure (two bowel perforations), but unrelated to the mesh itself. One death was related to complications from removal of eroded mesh. Adverse events associated with SUI sling procedures included pain, mesh erosion, infection, urinary problems, organ perforation, incontinence recurrence, bleeding, dyspareunia, neuromuscular problems and vaginal scarring.[4]

In 2011, FDA also undertook a systematic evaluation of the safety and effectiveness of surgical mesh to repair stress urinary incontinence based on the peer-reviewed scientific literature from January 1996 to April 2011. The results of this evaluation were included in FDA's Executive Summary document prepared for the Obstetrics & Gynecology Devices Advisory Committee Meeting on September 8-9, 2011.[5] Among the studies reviewed were 187 that evaluated surgical mesh for the treatment of SUI and 13 that used mesh for the treatment of both SUI and POP. There were 82 randomized controlled trials with at least one arm randomized to surgical mesh for the treatment of SUI and 105 observational studies that included at least one group of patients using surgical mesh for treatment of SUI. "The most commonly studied procedure using mesh for SUI repair was the TVT procedure, followed by the TOT procedure."[6] **Very few studies had follow-up assessments past 36 months, with the vast majority of information heavily weighted from the perioperative period (intraoperative to 48 hours postoperative) to one year postoperative**.[7] (Emphasis added.)

While there are a variety of minimally invasive synthetic slings for SUI and variations in the placement method, these slings appear overall to be as effective as open retropubic colposuspension. Notably, objective SUI cure rates for open colposuspension at one year range from 69% to 88%; cure rate appears to decline by 15-20% at greater than five years. As regards

[4] FDA Executive Summary: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence, Obstetrics & Gynecology Devices Advisory Committee Meeting, Sept. 8-9, 2011.
[5] *Id.*
[6] *Id.*
[7] *Id.*

placement method for minimally invasive synthetic slings, "[t]he bottom-to-top retropubic approach appeared to be more effective in the short term compared to top-to-bottom retropubic approach. Monofilament tape was more effective compared to multifilament tape. Objective and subjective cure rates were high for both transobturator and retropubic slings, with a slight advantage going to retropubic approach."[8]

Most commonly reported adverse events included erosion, dyspareunia, infection, pain, urinary problems (including *de novo* SUI, urgency, frequency, and overactive bladder), and re-surgery. These findings in the literature are consistent with the adverse events reported through the MAUDE database, discussed above.[9]

Notably, urinary problems from 6 months postoperatively to 60 months postoperatively were reported in 9-17% of all women who had SUI treated with surgical mesh. With time there were apparent increases in the proportion of women reporting urinary problems, re-surgery (range: 2.5% at 6 months postoperatively to 6.2% at 12 months postoperatively), and any infection (5.1% perioperatively to 27.6% at 60 months postoperatively).[10]

Erosion rates ranged from 0.25% to 4% from 6 months postoperatively to 60 months postoperatively, with no apparent trend. "Weighted rates of reported pelvic or vaginal pain ranged from 22.2% at 60 months to 1.6% at 36 months but more consistently averaged at about 5%. Neuromuscular adverse events were reported at a rate of 1% or less over the follow-up measurement periods. Dyspareunia rates ranged from a high of 13.7% at 60 months to 0.64% at 12 months."[11] Groin pain was reported as another risk of minimally invasive synthetic slings.[12] **Notably, the higher rates of these complications observed longer-term emphasize the importance and the necessity of conducting clinical studies with long-term follow-up.**

Perioperative complications reported most commonly included the following: organ perforation, (including bladder, urethral, vaginal, and bowel perforation), with a 3.9% weighted average across the literature; hemorrhage, occurring among 31.7% of patients; and hematomas, reported in 1.0% of patients. Of note, there were no clear definitions of hemorrhage and hematoma across the literature and, thus, clinically significant conclusions cannot be drawn from the reported rates. Hematomas were reported up to 12 months post surgery in 1.5% of patients.[13]

FDA concluded that "all minimally invasive synthetic slings (including mini-slings) are associated with risk of failure as well as patient injury" and, based on systematic review of the scientific literature and adverse event reports in the MAUDE database, "there is potential for serious complications with mesh products indicated for SUI repair." **As late as 2011, FDA reported concern that** "**safety outcomes may not have been comprehensively evaluated by RCTs to date and that the safety of SUI repair with mesh needs to be further considered in evaluating the overall risk to benefit profile of these products.**"[14] (Emphasis added.)

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[8] FDA Executive Summary: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence, Obstetrics & Gynecology Devices Advisory Committee Meeting, Sept. 8-9, 2011, page 36.
[9] *Id.*, page 38.
[10] *Id.*, page 38.
[11] *Id.*, page 39.
[12] *Id.*, page 43.
[13] *Id.*, page 39.
[14] *Id.*, pages 43-44.

FDA's Urogynecologic Surgical Mesh Implants website, last updated March 27, 2013, regarding Information for Health Care Providers for SUI, continues to advise clinicians "that there is **limited information about outcomes after one year**."[15]

As of January 4, 2016,[16] approximately 12 and 18 years after TVT-O and TVT, respectively, became eligible for sale, the "**FDA continues to assess the safety and effectiveness of urogynecologic surgical mesh devices**. Specifically, the FDA has:

- Reviewed and analyzed published literature, Medical Device Reports (adverse event reports) submitted to the FDA, and postmarket information submitted to the FDA.
- Conducted epidemiological research on the safety and effectiveness of surgical mesh, as a part of [the Agency's] **effort to better understand possible adverse events associated with surgical mesh for SUI** and POP.
- **Collaborated with professional societies and other stakeholders to fully understand** the postmarket performance of urogynecologic surgical mesh devices, and **the occurrence of and signs and symptoms associated with specific adverse events including low frequency but life-altering adverse events that may occur following** both **SUI** and POP **repair with surgical mesh**."
  (Emphasis added.)

C. 2nd International Urogynecological Association Grafts Roundtable Publishes Consensus on Need for Research and Minimum Standards for Mesh Use in Transvaginal Procedures

In 2012, the consensus of the 2nd International Urogynecological Association Grafts Roundtable conference (2010) was published on the subject of "[o]ptimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery,"[17] which noted that numerous new implants and ancillary devices had been introduced to the market in the prior 10 years "with **little or no clinical data or research**."[18] The authors proposed that **minimum standards should be demanded for new products prior to marketing**, including accurate data on the physical properties of the product, data on biological properties obtained following implantation in high-quality animal studies, anatomical studies on cadavers, and "**upfront clinical studies** followed by a compulsory registry on the first 1,000 patients implanted. Ideally, **manufacturers should support well-designed prospective (randomized) clinical trials that can support the claimed benefits of the new product**."[19] (Emphasis added.)

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[15] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345221.htm

[16] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262301.htm

[17] Slack M et al. A standardized description of graft-containing meshes and recommended steps before the introduction of medical devices for prolapse surgery (data presented at 2nd IUGA Grafts Roundtable June 2010). Int Urogynecol J 2012;DOI 10.1007: s00192-012-1678-2.

[18] *Id.*

[19] *Id.*

IV. CHANGES TO INSTRUCTIONS FOR USE (IFU): 2014-2015

In a letter dated March 24, 2014, the Therapeutics Products Directorate, Medical Devices Bureau, Health Canada, requested Johnson & Johnson Medical Products to provide Additional Information under Section 39 of its *Medical Devices Regulations* in regards to the company's "*Surgical Meshes for Stress Urinary Incontinence*," remarking that information recently brought to the Bureau's attention indicated that these devices "may not meet the safety and effectiveness requirements of the *Medical Devices Regulations* (the Regulations)."[20] Specifically, as it pertains to the subject matter of this Supplemental Report, Health Canada requested up-to-date labeling to include, but not limited to, the following potential complications/adverse events, advising that "[c]linical evidence has demonstrated that the use of surgical mesh for the treatment of stress urinary incontinence (SUI) has the potential to lead to [these] adverse events":

> "acute or chronic pain in the groin, thigh, pelvic and/or abdominal area; mesh extrusion, exposure or erosion; infection; voiding dysfunction; dyspareunia; neuromuscular damage; organ perforation; recurrence of incontinence; bleeding or hemorrhage; vaginal scarring and/or tightening; and mesh contraction and shrinkage. In addition, one or more revision surgeries may be necessary to treat these complications, while some complications may not always be completely corrected."[21]

Subsequent to this request, over the next approximately 14-15 months, Ethicon undertook to revise its professional and patient labeling globally for the TVT family of products, notably, in response not only to Health Canada but also to the Australian TGA's (Therapeutic Goods Administration) "URGENT" request for changes to labeling on October 17, 2014.[22] Specifically, TGA advised Ethicon that the TVT IFU needed to appropriately identify risks and detailed items that were either not already included and/or were not sufficiently prominent in the IFU. The matters to be addressed in the IFU included a clear discussion of risk of erosion in a prominent section, with comment regarding patient selection and factors that may increase the likelihood of complications such as erosion. Additionally, TGA requested that the IFU include a **complete description of all known complications**, including ongoing pain that may not be resolved on explant and other complications identified in the clinical literature, risk assessment documentation, and post-market data submitted to TGA in relation to the TVT. TGA further noted that these deficiencies "are considered to be breaches of compliance with one or more of the Essential Principles."[23] (Emphasis added.)

The revised IFUs became available on Ethicon's physician website on May 1, 2015, and were implemented in production in September 2015. The revised TVT family of products patient brochure became available on the physician website on May 4, 2015.[24]

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[20] ETH.MESH.16357665-666: March 24, 2014, Letter to Jerry Gee, Regulatory Affairs Specialist, Johnson & Johnson Medical Products, Markham, ON, from Medical Devices Bureau, Health Canada, Re: Request for Additional Information under Section 39 of the *Medical Devices Regulations*.
[21] ETH.MESH.16357665 at 665-666: *Id*.
[22] Dr. Martin Weisberg November 12-13, 2015, deposition: Exhibit D-9: 6-page document labeled "Chronology."
[23] ETH.MESH.24257904 at 911-914: Email October 17, 2014, from Patrick O'Meley, TGA, Subject: for your URGENT attention – Urogynaecological Surgical Mesh Review – Outcomes and actions.
[24] *Id*.

According to the "Updated IFU Index and Production Bates Range Chart" produced by Ethicon on November 6, 2015, there was one update to the TVT IFU (in use 12/9/14 through 8/31/15) and one update to the TVT-O IFU (in use 12/15/14 through 9/16/15)[25] since the time of my prior Reports regarding these products. Notably, there were no changes in those IFUs regarding the listing of adverse reactions as compared to IFUs in previous use. (Reference my TVT October 14, 2013, and June 12, 2014, Reports and July 17, 2014, and April 24, 2015 [First Supplemental] TVT-O Reports.) The safety information missing from prior IFUs, discussed in my prior Reports, persisted through the implementation of the 2015 revised IFUs for both products.

It is noteworthy that essentially all of the risk information that Health Canada requested Ethicon to add to the TVT and TVT-O IFUs was specified in my prior Reports (dating back to October 14, 2013, for my initial TVT Report) as safety information that was missing from the product IFUs. Of further note, TGA requested inclusion of all known complications identified in the clinical literature, risk assessment documentation, and post-market data, which were sources that I also evaluated to assess safety information missing from the product IFUs. Thus, both Health Canada's request and TGA's request for labeling changes provide corroboration from authoritative bodies of my prior opinions as regards missing safety information.

Additionally, Ethicon added a number of other adverse reactions or warnings that I had enumerated as missing safety information in my prior Reports to the revised IFUs implemented in 2015. Although these revised IFUs included much of the safety information specified as missing from IFUs in my prior Reports, my opinions remain the same as regards other labeling deficiencies or safety information that I previously specified as missing but which was not included in the 2015 revised IFUs.

V. ADVERSE MEDICAL DEVICE EVENT REPORTING: MAUDE DATABASE

Adverse event databases, such as the MAUDE Database, provide real world clinical experience that provide useful information about device safety and performance. This information should be considered as part of the ongoing clinical evaluation and risk analysis process for the life cycle of the device, and actions should be taken as appropriate to manage risk, e.g., updating safety information in the Instructions for Use. (Reference Exhibit 1, Section II.G.) Accordingly, Exhibit 2 provides a current overview of the results of MAUDE database searches for total number of medical device reports from 1999 through 2015 for Ethicon and a number of competitor surgical mesh devices marketed for the repair of SUI and POP. The significance of the large number of adverse event reports is highlighted by the industry-accepted recognition that there is vast underreporting of device-related problems, with estimates that as few as 1 in 100 medical device reportable events is actually reported. (Reference Exhibit 1, Section III.)

[25] In re: Ethicon, Inc. Pelvic Repair System, Products Liability Litigation, In re: Pelvic Mesh/Gynecare Litigation, Updated IFU Index and Production Bates Range Chart, Produced to Plaintiffs on 11/6/15 Pursuant to Protective Orders (Ethicon MDL No. 2327 and New Jersey Litigation, Case No. 291 CT).

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Peggy Pence

Peggy Pence, PhD, RAC, FRAPS

March 2, 2016

Date